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EXAMINER

KRUSE, DAVID H

ART UNIT PAPER NUMBER

1638

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/749,601

Applicant(s)

NICOLAIDES ET AL.

Examiner

David H Kruse

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 November 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-125 is/are pending in the application.

4a) Of the above claim(s) 3,4,6-14,22-30,37-45,48-55,57-76,80-82 and 86-125 is/are withdrawn from consideration.

- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,5,15-21,31-36,46,47,56,77-79 and 83-85 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 04/01/01 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group III, claims 1, 2, 15-21, 31-36, 46, 47, 56, 77-79 and 83-85, in Paper No. 15, filed 27 November 2002 is acknowledged. The traversal is on the ground(s) that Applicants submit that the groups identified are connected in design, operation or effects. Applicant also argues that because Groups I-XII are similarly classified that it would not be an undue burden to examine Groups I-XII together (pages 2-3 of the response). This is not found persuasive because each of Groups I-XII are directed to a method of making a hypermutable plant cell with a different polynucleotide encoding a different mismatch repair polypeptide. Consequently, even though each method has similar effects, the product of each method is patentably distinct.

Applicant proposes joining groups related to the use of forms of the MutS gene, Groups I, VII, IX and XI, (page 3 of the response). The Examiner will examine the elected Group III directed to a method using a mammalian PMS2 gene. Similarly, Applicant's arguments on pages 3-6 of the Response are not found to be persuasive because Groups XIII-XXI are directed to method of using a MutL or MutS gene in a plant cell, or regulation of an endogenous gene in a plant cell, Groups XXII and XXIII are directed to plant transformation vectors that have separate utilities under 35 USC 101, Groups XXIV and XV are directed to isolated polynucleotides that have separate utilities under 35 USC 101, Groups XVI and XVII are directed to isolated proteins that

cannot be used in the elected method claims, and Group XXVIII is a distinct method from that of the elected invention.

The Examiner notes that Claim 5 should have been included in Group III, the elected invention, and will be examined with the elected invention.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 3, 4, 6-14, 22-30, 37-45, 48-55, 57-76, 80-82 and 86-125 are withdrawn from further consideration pursuant to 37 CFR § 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 15.

3. This application contains claims 3, 4, 6-14, 22-30, 37-45, 48-55, 57-76, 80-82 and 86-125 drawn to an invention nonelected with traverse in Paper No. 15. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR § 1.144). See MPEP § 821.01.

4. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR § 1.48(b) and by the fee required under 37 CFR § 1.17(i).

Information Disclosure Statement

5. The information disclosure statements filed 25 February 2002, 16 July 2001 and 16 August 2001 have been considered, signed copies are attached to this Office action.

Claim Objections

6. Claims 1, 2, 18, 19, 34, 47, 77, 83 and 84 are objected to because they comprise non-elected subject matter. Amendment of the claims to delete the non-elected subject matter is required.

7. Claim 56 is objected to under 37 CFR § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the instant case, claim 56 further limits a protein at claim 47, yet claim 47 does not recite a protein, but a mismatch repair gene. Amending claim 56 to further limit the mismatch repair gene of claim 47 would obviate this objection.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

9. Claims 17, 18-21, 31-33, 77-79 and 83-85 rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 17, 33 and 85 are indefinite because it is unclear if the claims are directed to a method of using a truncation mutation of a wild-type human PMS2 allele or to any mammalian PMS2 allele having a truncation mutation at the relative thymidine at nucleotide 424 of a wild-type human PMS2 allele, hence it is unclear what the metes and bounds of the claims are.

Claim 18 is indefinite because introducing a polynucleotide into a plant cell in a plant produces a transgenic plant cell it does not produce a transgenic plant *per se*. Hence, it is unclear what the metes and bounds of the claimed invention are.

Claim 19 is indefinite because claim 18 already recites a transgenic plant and it is unclear what the metes and bounds of "a mature transgenic plant" are. Claims 20, 21, 31, 32 and 33 are also indefinite because said claims do not obviate the indefiniteness of claim 19.

Claim 77-79 and 83-85 are indefinite because claim 67, directed to a non-elected invention, is a method of generating a mutation in a gene of interest in a plant, and not to a method of producing a hypermutable transgenic plant. Hence, it is unclear what the metes and bounds of the claimed invention are.

10. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1, 2, 5, 15-21, 31-36, 47, 77, 78 and 83-85 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The issue of indefiniteness of claims 17, 33 and 85 is discussed above.

Applicant claims a method of making a hypermutable cell comprising introducing into a plant cell a polynucleotide comprising a dominant negative allele of a mismatch

repair gene, whereby the cell becomes hypermutable. Applicant additionally claims that said gene is a mammalian PMS2 gene, a truncation mutation of said gene, and compositions and plant comprising said plant cell.

Applicant describes a method of making a hypermutable plant cell by transforming said plant cell with a gene encoding a truncated human PMS2 protein, said human PMS2 gene having been truncation mutation at codon 134 corresponding to a thymidine at position 424 of the wild-type human PMS2 gene (pages 17-21 of the specification).

Applicant does not describe other dominant negative alleles of other mismatch repair genes that can be used in the claimed method or can be used to make the claimed compositions or plants. In addition, Applicant does not describe other truncation mutations of such genes that can be used in the claimed method and compositions.

Hence, it is unclear from the instant specification that Applicant was in possession of the invention as broadly claimed.

See also, MPEP § 2163 which states that the claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description

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purposes, even when accompanied by a method of obtaining the claimed sequence. In the instant case the claims are only describe in terms of function as encoding a dominant negative allele of a mismatch repair gene, a mammalian PMS2 gene and a truncation mutation of said allele.

12. Claims 1, 2, 5, 15-21, 31-36, 47, 77-79 and 83-85 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of making a hypermutable plant cell comprising transforming said plant cell with a polynucleotide comprising nucleotide sequence that encodes the human PMS2 134 truncation mutation and plant cells and plants produced by said method, does not reasonably provide enablement for a method of making a hypermutable plant cell comprising transforming said plant cell with a polynucleotide comprising any dominant negative allele of any mismatch repair gene and plant cells and plants produced by said method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant claims a method of making a hypermutable cell comprising introducing into a plant cell a polynucleotide comprising a dominant negative allele of a mismatch repair gene, whereby the cell becomes hypermutable. Applicant additionally claims that said gene is a mammalian PMS2 gene, a truncation mutation of said gene, and compositions and plant comprising said plant cell.

Applicant teaches a method of making a hypermutable plant cell by transforming said plant cell with a gene encoding a truncated human PMS2 gene, said human PMS2

gene having been truncation mutation at codon 134 corresponding to a thymidine at position 424 of the wild-type human PMS2 gene (pages 17-21 of the specification).

Applicant does not teach other dominant negative alleles of other mismatch repair genes or other mammalian PMS2 mismatch repair genes that can be used in the claimed method or can be used to make the claimed compositions or plants. In addition, Applicant does not teach other truncation mutations of such genes that can be used in the claimed method and compositions.

In re Wands, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) lists eight considerations for determining whether or not undue experimentation would be necessary to practice an invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

Applicant has provided limited guidance for a method of making a hypermutable plant cell by introducing into said plant cell a polynucleotide comprising any dominant negative allele of a mismatch repair gene, especially any mammalian PMS2 gene as broadly claimed. In addition, Applicant has provided limited guidance for a method of using a truncation mutation of said mammalian PMS2 gene or any mismatch repair gene in the instant specification. At claims 16, 32 and 84, Applicant has provided limited guidance for how to make and use truncation mutations at codon 134 of any mammalian PMS2 gene as broadly claimed, the indefiniteness of claims 17, 33 and 85

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is discussed *supra* and thus it is unclear if all mammalian and/or wild-type PMS2 genes have a thymidine at nucleotide 424. The art teaches that when one or more of the minor proteins, such as the PMS2, is impaired that MMR function is retained or only partially perturbed because MSH3 and MSH6 have some functional redundancy and can compensate, at least in part, for the loss of the impaired protein (see Chang *et al* 2001, Genome Research 11(7): 1145-1146, especially page 1146, left column). In addition, Pang *et al* (1997, Molecular and Cellular Biology 17(8): 4465-4473) teach that a yeast Pms1p (amino acids 1-271) truncation mutation, yeast Pms1p being the functional equivalent of the mammalian PMS2, did not have a dominant negative effect (see Table 1 on page 4470). Thus, the art teaches that it is unpredictable whether an impaired minor protein such as the PMS2 will actually impair MMR function in a cell without empiric evidence. Hence, it would have required undue trial and error experimentation by one of skill in the art at the time of Applicant's invention to screen through a myriad of mammalian PMS2 negative alleles of the mismatch repair gene, truncation mutations, or truncation mutations at codon 134 to identify those alleles that could be used in the instant method to make hypermutable plants as broadly claimed.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

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14. Claims 1, 2, 18, 19, 34, 47 and 77 are rejected under 35 U.S.C. § 102(a) as being anticipated by Doutriaux *et al* (WO 99/19492, published 22 April 1999).

Doutriaux *et al* disclose a method of making a hypermutable cell comprising introducing into a plant cell a polynucleotide comprising a dominant negative allele of a mismatch repair gene, whereby the cell becomes hypermutable. Doutriaux *et al* disclose that by overexpressing an AtMSH3 and/or an AtMSH6 gene, the associated AtMSH2 protein is bound up in the plant cell and does not function in mismatch repair (see page 9, 2nd paragraph and page 21, section D). Applicant states that a dominant negative allele of a mismatch repair gene causes a mismatch repair defective phenotype even in the presence of a wild-type allele in the same cell (see page 7, 2nd paragraph of the specification). Doutriaux *et al* disclose a method of regenerating a transgenic plant as claimed in claims 18 and 19 (see claims 18 and 19 of Doutriaux *et al*). Doutriaux *et al* inherently disclose the homogenous composition of cultured, hypermutable, plant cells at claim 34, and the hypermutable transgenic plant at claim 47. Hence, Doutriaux *et al* has previously disclosed all of the claim limitations.

Conclusion

15. Claims 5, 15-17, 20, 21, 31-33, 35, 36, 46, 56, 78, 79 and 83-85 are free of the prior art which neither teaches nor fairly suggests a method for making a hypermutable plant cell by introducing a polynucleotide encoding a dominant negative allele of a mammalian PMS2 mismatch repair gene or a truncation mutation thereof, or a plant cell or plant comprising said polynucleotide.

16. No claims are allowed.

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17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David H. Kruse, Ph.D. whose telephone number is (703) 306-4539. The examiner can normally be reached on Monday to Friday from 8:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Amy Nelson can be reached at (703) 306-3218. The fax telephone number for this Group is (703) 872-9306 Before Final or (703) 872-9307 After Final.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group Receptionist whose telephone number is (703) 308-0196.

A handwritten signature in black ink, appearing to read "Amy Nelson", with a stylized flourish at the end.

David H. Kruse, Ph.D.
5 February 2003

AMY J. NELSON, PH.D
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